METHOD AND APPARATUS FOR MINIMIZING SPECTRAL INTERFERENCE DUE TO WITHIN AND BETWEEN SAMPLE VARIATIONS DURING *IN-SITU* SPECTRAL SAMPLING OF TISSUE

BACKGROUND OF THE INVENTION

The invention relates to spectral analysis of biological analytes. More particularly the invention relates to an apparatus and method for minimizing spectral interference due to within and between sample variations during *in-situ* spectral sampling of tissue.

DESCRIPTION OF RELATED ART

Non-invasive, near IR diffuse reflectance measurement of glucose in human tissue requires sampling techniques that limit the degree of sampling error. The heterogenous and dynamic nature of living skin leads to sampling uncertainty in *in-vivo* measurements. Sampling differences may arise due to variable chemical composition and light scattering properties in tissue. Because glucose is not uniformly distributed in tissue, a variation in the volume of tissue sampled is likely to lead to a variation in the strength of the glucose signal; the overall glucose concentration in tissue of blood remains constant. Variations in the placement and replacement of the fiber optic probe at the measuring surface can lead to changes in the optical sampling volume. A change in optical sampling leads to a variation in the glucose signal while blood glucose concentration remains unchanged.

Near infrared (NIR) tissue spectroscopy is utilized to irradiate the skin on the underside of a subject's extremity and estimate blood levels of biological analytes using a multivariate mathematical model. Mathematical analysis is used to extract significant spectral information about the net analyte signal. A large data set of samples from each subject is required to ensure a robust multivariate model. Spectral interferences within a measurement and between measurements lead to a decrease in the net analyte signal. As

indicated above, sources of spectral interference include, but are not limited to, variation in location of the sample site and amount of pressure applied at the sample site. Furthermore, the physiological response of the tissue to contact with the measurement instrument is a significant source of sample variability. It is essential that known sources of spectral interference be minimized if a robust calibration model is to be developed.

P. Cooper and T. Barker, *Individual calibration of blood glucose for supporting noninvasive self-monitoring blood glucose* (sic), PCT Application Ser. No. WO 98/37805 (February 26, 1997) and J. Griffith, P. Cooper, T. Barker, *Method and apparatus for non-invasive glucose sensing*, U.S. Patent No. 6,088,605 (July 11, 2000) describe methods and apparati for non-invasive blood glucose determination. Spectroscopic samples are gathered at the subject's skin surface using a noninvasive glucose monitor. During sampling, the skin surface is repeatedly moved relative to the sampling probe, so that several samples are gathered, each from a slightly different measurement site. Provision is also made for raising and lowering the arm in a controlled manner relative to the sampling probe. While both references recognize that is desirable that the spectra making up calibration sets, test sets and subsequent sample spectra, be as free of noise from sampling factors as possible, they do not actually attempt to eliminate sampling error at the time of measurement by sampling in a reproducible manner. Rather, they attempt to ameliorate sampling error by averaging it out over several measurements. Furthermore, while they recognize that placement and pressure variations are important sources of spectral interference, they fail to address the problem of spectral interference caused by the physiological response of the subject's skin to contact with the measurement instrument. The described apparatus has no provision for adjusting the size and dimensions of the apparatus to individual subjects by providing replaceable components in a variety of shapes and sizes.

In a co-pending, commonly-assigned application, T. Blank, G. Acosta, M. Mattu, S. Monfré, *Fiberoptic probe placement guide*, U.S. Patent Application

Ser. No. 09/563,782 (May 2, 2000) describe a placement guide for a fiber optic probe that comprises a mounting element shaped and dimensioned to approximate the contour of a subject's extremity, upon which a tissue measurement site is located. The mount includes a probe aperture into which the fiber optic probe is inserted to make contact with the tissue measurement site. While contact with the skin in the immediate vicinity of the measurement site is avoided, the mounting element rests atop the limb during use, possibly causing temperature transients near the tissue measurement site, due to physiological responses of the skin to contact with the placement guide and the probe. The guide is positioned by aligning cross hair slots around the aperture with crosshairs drawn on the subject's skin, rendering the probe guide better suited to short-term use in laboratory settings. The disclosed probe guide doesn't fully contemplate the importance of minimizing spectral effects related to pressure variations, since the fiber optic probe is inserted into the probe aperture as the mount rests atop the limb bearing the tissue measurement site, allowing for the possibility of pressure variations.

Another co-pending, commonly-assigned U.S. Patent application, K. Hazen, G. Acosta, *Apparatus and method for reproducibly modifying localized absorption and scattering coefficients at a tissue measurement site during optical sampling*, U.S. Patent Application Ser. No.09/631,440 (August 2, 2000) describes an apparatus for modifying localized absorption and scattering coefficients by controlling the pressure applied to a tissue measurement site by an analyzer during optical sampling. The applied pressure may be maintained at a constant level, or it may be varied in a controlled, reproducible manner as a function of time, thus allowing absorption and reduced scattering coefficients to be varied in a controlled, reproducible manner. The device provides a placement guide for a limb bearing a measurement site that permits placement of the measurement site and pressure on the measurement site by the instrument to be reproducibly controlled. The described apparatus fails to contemplate, the importance, however of minimizing contact of the apparatus with the extremity bearing

the measurement site to minimize the physiological response of the skin at the measurement site to contact with the apparatus. Furthermore, replaceable components in a variety of shapes and sized to adjust the apparatus to individual subjects are not provided.

It would be a great advantage to provide an apparatus and method for minimizing spectral interference during *in-situ* spectral sampling of tissue that enables the measurement site to be reproducibly positioned in relation to an optical coupling means, so that spectral interference related to placement and pressure variations is minimized. It would be a further advantage to provide such an apparatus in a minimal contact configuration, so that spectral interference related to contact of the measurement site with the apparatus is minimized. It would provide significant benefit if the apparatus were customizable to individual subjects; for example, by providing replaceable components custom-fabricated to a subject, or by providing replaceable components in a variety of shapes and sizes so that the apparatus may be adapted to subjects of different size or physiognomy.

SUMMARY OF THE INVENTION

The invention provides an apparatus and method for reproducibly interfacing a living tissue sample to the measurement probe of a spectrometer instrument *in-situ*, so that spectral interference related to sampling variations is minimized. A subject interface includes a base element having a plurality of supports mounted thereupon, each support providing a registration point on a subject's limb bearing a tissue measurement site. A probe aperture in the base element is provided through which an optical coupling means, such as a fiber optic probe, contacts the measurement site. In a preferred embodiment of the invention, elbow, wrist and hand supports are provided, spaced at ergonomically optimal intervals along the length of the base element. During use, the interface module is positioned on top of a spectrometer instrument with the measurement probe protruding upward

toward the measurement site on the underside of the subject's arm. The supports have a minimal footprint so that contact with the skin of the arm is minimized. The interface module is adjustable, allowing it to be customized to any subject. In one embodiment, the supports are custom-fabricated to the subject. In another embodiment, the supports are provided in a variety of shapes and sizes. The various shapes and sizes may be combined to adjust the interface module to any subject. During use, the subject rests their arm on the support elements, so that the arm is reproducibly positioned and supported. Thus, spectral interference due to placement and pressure variations is minimized. The minimal contact of the support elements with the skin of the arm minimize spectral interference due to contact-induced temperature transients at the skin surface of the measurement site.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides a plan view of a subject interface module, according to the invention; and

Figure 2 provides a side elevation of the subject interface module of Figure 1, according to the invention.

DETAILED DESCRIPTION

Spectroscopic estimation of blood analyte concentration is hampered by spectral interferences. Living human tissue is dynamic by nature and continuously undergoes changes in response to the environment. Physiological changes take place even while light is penetrating the tissue. Furthermore, shifts in the environment, such as temperature changes induce corresponding physiological changes in skin tissue. Interferences in spectral measurements at a tissue measurement site may be due to a variety of factors, among them skin temperature transients, variations in pressure applied to the skin at the measurement site, variations in tissue state,

variations in positioning of the site relative to the spectrometer instrument, and others. Such sampling variations cause a reduction in the net analyte signal, which prevents the development of robust calibration models necessary for accurate estimates of biological analyte concentration. A novel subject interface module couples the subject's extremity bearing the tissue measurement site to the measurement probe of the spectrometer in such a way as to minimize spectral interferences within and between measurements. The subject interface module incorporates a minimal contact design to support and position the subject's extremity in a controlled and reproducible manner, thus addressing the following sources of spectral interference:

- Within sample temperature transients. Living tissue undergoes a physiological temperature response upon coming into contact with environmental surfaces. Skin temperature may rise or fall, or a combination of both, depending on the temperature and heat capacity of the object the skin comes into contact with. Large skin temperature transients lead to increased spectral interference. The minimal contact subject interface module design provides support for the subject's extremity while minimizing the physiological response due to contact at the measurement site.

- Pressure applied to the extremity at the measurement site. Pressure applied to living tissue impacts the localized thickness of the skin. Varying the force applied at the measurement site changes the tissue volume sampled by the beam of light emitted from the measurement probe. The subject interface module is designed to maintain consistent pressure in a reproducible fashion between the extremity and the measurement probe, thereby minimizing between sample variations in the tissue volume.

- Positioning of the extremity in relation to the instrument. The subject interface module provides replaceable support elements to ensure

that the subject's extremity is in a natural position and properly aligned with the measurement probe. The support elements may be custom fabricated for a subject or universal support elements in various shapes and sizes may be combined in various ways to adjust the subject interface module to any subject.

The support elements, along with the correct method of seating the extremity in the interface module, ensure that the extremity is reproducibly positioned and supported and that skin temperature transients due to contact of the extremity with the interface module are minimized.

In a preferred embodiment, the subject interface module is adapted to receive the arm of a human subject during noninvasive blood analyte determination using spectral analysis, such as Near IR. However, other embodiments consistent with the spirit and scope of the invention will be apparent to those skilled in the art of spectroscopic sampling techniques. For example, the principles of the invention may be employed to develop subject interface modules for veterinary use, or sample interface modules for use in spectroscopic analysis of fruits and vegetables. Furthermore, while the preferred embodiment is intended for use on live human subjects, it could also be used on the non-living, by pathologists for example.

Figure 1 shows a plan view of the subject interface module 10 according to the preferred embodiment. A base element 11, having a top surface and a bottom surface is provided. During use, the subject interface module is placed on top of a spectrometer instrument (not shown). An aperture 12 in the base 11 provides a measurement probe (not shown) access to the underside of the subject's arm when the arm is seated in the interface module 10.

In this way, the subject interface module fits around a stationary measurement probe that is used to irradiate the skin. The co-pending U.S. Patent Application Ser. No. 09/631,440, *supra*, which is hereby incorporated

by reference in its entirety, provides a detailed description of such a fiber optic probe. Light emitted from the probe travels through the heterogeneous layers of the tissue, where it is reflected and absorbed.

Elbow 13, wrist 14 and hand supports 15, are attached to the base element 11. As previously mentioned, the supports are replaceable. That is, they are easily removed and replaced with others. The supports may be custom-fabricated for a subject and attached to the base element when that subject is sampled. In another, equally preferred embodiment of the invention, universal supports are provided in a variety of shapes and sizes to accommodate a broad cross-section of individuals. The elbow support 13, attached at the proximal end of the base element 11, is molded such that it provides a cup-shaped depression 20 that closely mirrors the geometry of the elbow. In the case of custom-molded supports, the elbow support provides a near-exact negative impression of the subject's elbow. Universal elbow supports are provided in a variety of sizes to accommodate elbows of varying diameter. The universal elbow supports further include shims (not shown) of varying thickness, that may be placed between the base element and the elbow support, thereby allowing the height of the elbow support to be adjusted. It is desirable to adjust the height of the elbow support to accommodate arms of varying diameters, and so that downward pressure of the arm on the fiber optic probe may be varied in a controlled manner. Various methods of attaching the elbow support to the base may be used. Any method that allows the support to be securely attached and easily removed would be suitable; for example, a layer of pressure-sensitive adhesive applied to the support or to the base, VELCRO, various snap-in mechanisms or latching systems.

Toward the distal end of the base 11, a wrist support 14 provides a means of supporting the subject's wrist at the desired height while maintaining the arm in a natural position. A natural arm position is important for maintaining the subject's comfort, thereby minimizing the possibility that they will move the arm during sampling. The wrist support 14 is removably attached to a carrier

element 30 (Figure 2) mounted in parallel slots 17 in the base element 11 that permit the carrier element to be moved back and forth by sliding. In this way, the horizontal position of the wrist support can be adjusted. Various methods of attaching the wrist support to the carrier element are possible, for example, a bayonet type mechanism, a snapping mechanism or a threaded mechanism. During use, the wrist is rested on the wrist support such that it is received by an ergonomically shaped depression 19 that mirrors the contour of the wrist. As with the elbow support, the wrist rest may be custom fabricated for a particular subject, or universal supports may be provided in a variety of heights and contours to accommodate a broad cross-section of the subject population.

A hand support assembly 15 protrudes from the distal end of the base 11. In one embodiment of the invention, the hand support assembly is provided as a single structure. In an alternate embodiment of the invention, a hand support 16 is removably attached to a second carrier element 21. In either case, the hand support assembly 15 is mounted in a second pair of parallel slots 18, that allows the entire assembly to be retracted and extended in a slideable fashion, according to the length of the subject's arm. As with the other supports, the hand support is ergonomically contoured to mirror the shape of the hand and to support the hand such that a comfortable, natural hand position is encouraged. During use, the hand is rested on the hand support.

Indicators, such as graduated scales (not shown), or common measurement devices allow the horizontal position of the wrist and hand supports to be measured and recorded so that they may reproduced at any future time.

Patterns of circular openings 31 in the base provide an opportunity for free movement of air in the vicinity of the tissue measurement site. Additionally, the pairs of parallel slots 17 and 18 serve a second function of skeletonizing the base element as much as possible to facilitate air circulation. Thus, the possibility of skin temperature transients secondary to contact with the

subject interface guide is further minimized.

In its current embodiment, the base element is fabricated from ABS (acrylonitrile butadiene styrene) plastic using conventional injection molding techniques, however other thermoplastic polymers would also be suitable. The supports may be fabricated from the same material, or they may be fabricated from an elastomeric substance that provides a resilient surface, such as RTV (room temperature vulcanizing) silicone putty. It is highly preferable that the invention be fabricated from thermally stable materials. That is, they tend to maintain a stable surface temperature.

Through the use of the supports, contact with the interface module by the subject's arm is restricted to the registration points where the supports contact the arm. In this way, thermal transients at the skin surface due to contact with the measuring instrument are greatly minimized.

In the case of custom-fabricated supports, reproducibly supporting and positioning the arm for future samples is readily achieved by attaching the subject's supports and restoring the wrist and hand supports to the previously recorded position for that subject. In the case of universal supports, the sizes and shapes of the parts used to achieve the desired placement for that subject are recorded, and those same parts are used for future samples.

Once the subject's arm is properly positioned, sampling occurs by directing light emitted from a radiation source toward the tissue measurement site through a fiber optic probe. The light that is reflected back is collected and represents a data point that contains spectral information about the tissue volume it has traveled through. Multiple data points comprise a data set, which is required for calibration development. By using the subject interface module to position the subject's arm, spectral interferences from the sampling variations already described are greatly minimized, thus facilitating the process of obtaining reproducible data points. Minimizing interferences

optimizes the signal-to-noise ratio, allowing the development of robust calibration models, which in turn produces more accurate estimations of analyte concentration.

EXPERIMENT

An experiment was performed to analyze skin temperature variation due to arm contact with a subject interface module. Several subject interface module contact configurations were investigated to improve the subject interface module design from a thermal stability perspective. The results of this investigation show that minimal contact between the subject interface module and arm is desirable.

Introduction

Previous investigations have shown that the amount of contact between the subject interface module and an arm has a significant influence on the skin temperature transients that occur during the course of a noninvasive measurement. A full contact subject interface module was modified so that the only contact points between the arm and the subject interface module are at the elbow, wrist, hand, and the spectral measurement site. In addition, this modified subject interface module provides for custom supports at the contact points through the use of a mold that can be made for each subject.

Experimental

Prior to the modifications made to the subject interface module, skin temperature response to subject interface module contact was collected using seven subjects with a full-contact subject interface module. The same subjects were also tested on a third subject interface module, also providing minimal contact at the elbow, wrist, and hand.

Noninvasive spectra were collected for seven subjects using a fiber optic coupled spectrometer instrument with the modified subject interface module.

A YSI (YELLOW SPRINGS INSTRUMENTS of Yellow Springs OH) pediatric temperature probe was used to measure each subject's skin temperature close to the spectral measurement site. Ambient skin temperature was monitored prior to data collection to ensure a stable starting temperature. Four replicates were collected for each subject using lab software with a total of 16 spectra pairs per replicate. Temperatures were recorded for each forward raster scan during collection. The total scan time per replicate was approximately 2 minutes.

Results

Initial results from this study indicate a reduction in skin temperature transients with the modified subject interface modules. Table I presents the maximum temperature change for subjects tested along the subject's forearm over 90 second intervals on three different subject interface modules: the full-contact subject interface module, the first modified subject interface module (minimal contact), and the second modified subject interface module (minimal contact).

Table 1: Maximum temperature differences (T_{max} -T_{min}) over 90 seconds of contact

	Full-contact	**Modified** (to produce minimal contact) **full contact**	**Minimal contact**
	0.50	0.16	0.05
	0.50	0.21	0.20
	0.80	0.19	0.05
	0.90	0.19	0.10
	1.10	0.41	0.20
	0.75	0.16	0.30
	0.35	0.20	0.10
Average	0.70° F	0.217° F	0.143° F

Large temperature transients have been observed during approximately the first 30 seconds of subject interface module contact and, therefore, have been excluded from this analysis. It should be noted that due to the requirement of custom molds for the modified full-contact subject interface module, the subjects tested on the modified subject interface module were not all the same as those tested on the full contact and minimal contact

subject interface modules. Assuming the two populations are equal, an F-test at 99% confidence shows that there is a difference between the temperature range of the Full Contact subject interface module and the modified subject interface module. In addition, at 99% confidence, there is no difference between the modified full contact subject interface module and the minimal contact subject interface module.

Discussion

The analysis shows that arm contact on the modified full contact subject interface module leads to a smaller range of skin temperature transients than does the full contact subject interface module. The modified full contact subject interface module ranges are slightly higher than those of the minimal contact subject interface module. This could possibly be due to the differences in the amount of contact at the elbow support. The customized elbow supports used on the modified full contact subject interface module provide for more contact than the generic elbow support of the minimal contact subject interface module.

Although the invention has been described herein with reference to certain preferred embodiments, one skilled in the art will readily appreciate that other applications may be substituted without departing from the spirit and scope of the present invention. Accordingly, the invention should only be limited by the Claims included below.